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THE PATENTS ACT, 1970

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.....

.....In witness thereof

I have hereunto set my hand

Dated this the 24th day of August, 2004
02nd day of Bhadrapada, 1926 (Saka)

M.S. Venkataraman

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FORM - 2

THE PATENTS ACT, 1970

(39 OF 1970)

COMPLETE SPECIFICATION

(See Section 10)

TITLE OF INVENTION

"A novel intermediate of Moxifloxacin therefor and production method of the intermediate"

2. Matrix Laboratories Ltd, with its registered office at 1-1-151/1 , IV Floor , Sairam Towers, Alexander Road, Secundrabad, 500003, India an Indian Company

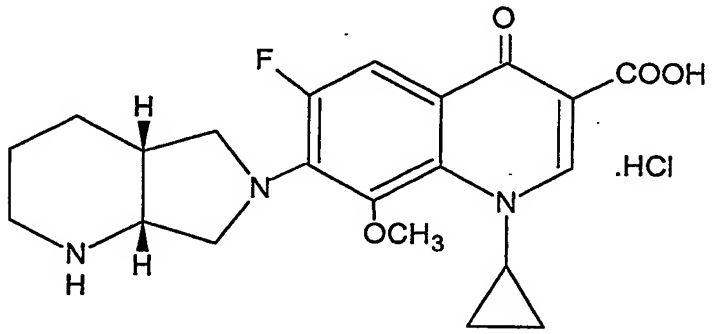
The following specification particularly describes the nature of the invention and the manner in which it is to be performed.

Field of the Invention: -

The present invention relates to a novel intermediate, (4aS-Cis)-(1-cyclopropyl-7-(2,8-diazabicyclo[4.3.0]non-8-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid-O^3,O^4)bis (acyloxy-O)borate and the process for its preparation

Background of the Invention: -

(4aS-Cis)-(1-cyclopropyl-7-(2,8-diazabicyclo[4.3.0]non-8-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid-O^3,O^4)bis (acyloxy-O)borate is an useful intermediate for the preparation of Moxifloxacin Hydrochloride namely (4aS-Cis)-1-cyclopropyl-7-(2,8-diazabicyclo[4.3.0]non-8-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid hydrochloride has the structure



Moxifloxacin Hydrochloride

Moxifloxacin is a fluoroquinolone broad spectrum antibacterial particularly against gram-positive bacteria significantly better than those of Sparfloxacin and Ciprofloxacin that was disclosed in European patent no's EP 350,733 and EP 550,903. Moxifloxacin has activity against gram-negative and Gram-positive organisms, including Streptococcus pneumoniae, Staphylococcus aureus, Pseudomonas aeruginosa, particularly against the respiratory disease-causing pathogens like Mycoplasma pneumonia, Mycobacterium tuberculosis, Chlamydia pneumoniae and the activity shown to be unaffected by B-lactamases.

US Patent No 5,157,117 discloses (1-Cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid-O^3,O^4)bis (acyloxy-O)borate and a process for its preparation by reacting the ethyl 1-cyclopropyl-6 ,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylate with Boric acid and acetic

anhydride in presence of zinc chloride and conversion to Gatifloxacin hydrochloride.

European Patent No's EP 350,733, EP 550,903 & EP 657,448 discloses preparation of Moxifloxacin by the condensation of 1-Cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-quinoline carboxylic acid or its esters with (S,S) 2,8-Diaza bicyclo[4.3.0]nonane in presence of a base, followed by conversion to hydrochloride.

It is a long felt of the industry to provide high yielding and cost effective process for the preparation of Moxifloxacin hydrochloride

Summary of the invention: -

The main object of the invention is to provide a process for the preparation of the novel intermediate (4aS-Cis)-1-cyclopropyl-7- (2,8-diazabicyclo[4.3.0]non-8-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid-O^3,O^4)bis (acyloxy-O)borate.

Another object of the invention is to provide a novel intermediate (4aS-Cis)-1-cyclopropyl-7-(2,8-diazabicyclo[4.3.0]non-8-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid-O^3,O^4)bis (acyloxy-O) borate for its use in the preparation for moxifloxacin hydrochloride .

Another object of the invention is to provide fingerprinting of the novel intermediate (4aS-Cis)-1-cyclopropyl-7-(2,8-diazabicyclo[4.3.0]non-8-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid-O^3,O^4) bis (acyloxy-O) borate using NMR, IR and x-ray diffraction.

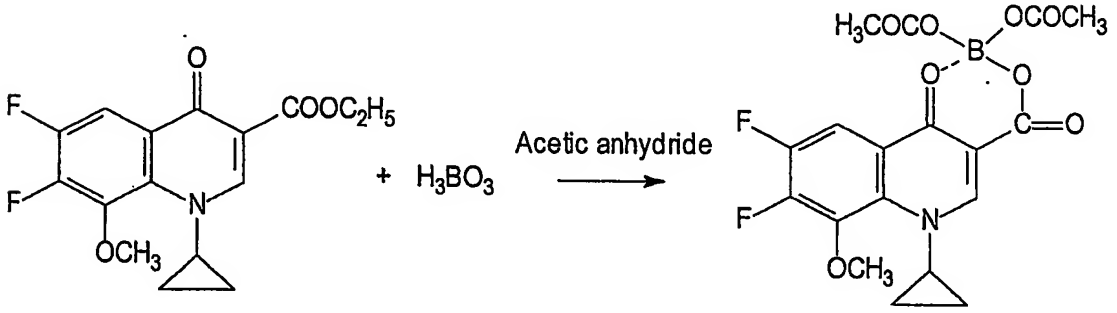
Yet, another object of the invention is to provide a process for the preparation of (1-Cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid-O^3,O^4)bis (acyloxy-O)borate without using the catalyst and its use for the preparation of (4aS-Cis)-1-cyclopropyl-7-(2,8-diazabicyclo[4.3.0]non-8-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid-O^3,O^4)bis (acyloxy-O)borate.

Accordingly, the present invention relates to a method for the preparation of novel intermediate (4aS-Cis)-1-cyclopropyl-7-(2,8-diazabicyclo [4.3.0]non-8-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid-O^3,O^4)bis (acyloxy-O)borate from the ethyl 1-cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylate. The reaction of ethyl 1-cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylate with boric acid and acetic anhydride without using any catalyst gives (1-Cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid-O^3,O^4)bis (acyloxy-O)borate which upon condensation in presence of a base(s) with (S,S)-2,8-diazabicyclo[4.3.0]nonane in organic polar solvent results the novel intermediate

(4aS-Cis)-1-cyclopropyl-7-(2,8-diazabicyclo[4.3.0]non-8-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid-O^3,O^4)bis (acyloxy-O)borate.

The reaction scheme is given below:

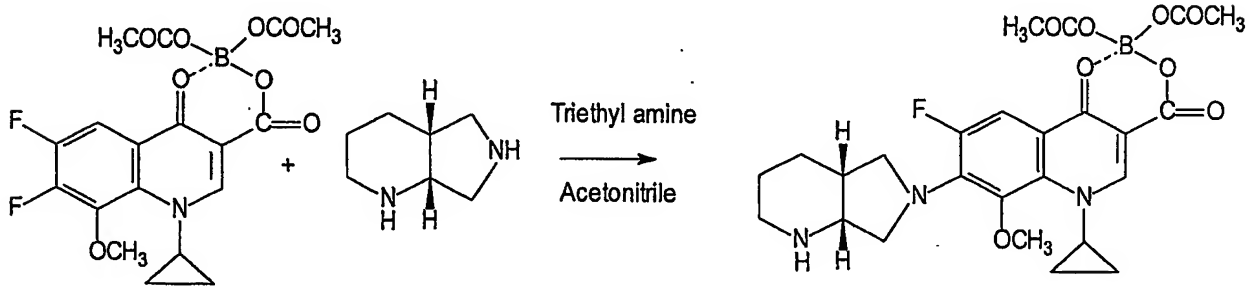
Stage-I



Ethyl 1- cyclo propyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinoline carboxylate.

(1- cyclo propyl-6,7- difluoro-1,4-dihydro-8- methoxy-4-oxo-3-quinoline carboxylic acid-O^3,O^4) Bis (acetate-O)-borate (Borate complex)

Stage-II



(1- cyclo propyl-6,7- difluoro-1,4- dihydro-8- methoxy-4-oxo -3-quinoline carboxylic acid-O^3,O^4)Bis (acetate-O)-borate (Borate complex)

[S,S]-2,8-diazabicyclo-[4.3.0]nonane

(1- cyclo propyl-6, fluoro-7(2,8-Diazabicyclo-nonane) 1,4-dihydro-8-methoxy-4-oxo-3 quinoline carboxylic acid-(O^3,O^4) bis (acetate-O)-borate

Brief description of the drawings: -

Fig.1: X-ray diffraction pattern of the (4aS-Cis)-1-cyclopropyl-7-(2,8-diazabicyclo[4.3.0]non-8-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid-O^3,O^4)bis (acyloxy-O) borate.

Fig.2: FTIR spectrum of the (4aS-Cis)-1-cyclopropyl-7- (2,8-diazabicyclo [4.3.0] non-8-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid-O^3,O^4)bis (acyloxy-O)borate.

Fig.3: NMR spectrum of the (4aS-Cis)-1-cyclopropyl-7-(2,8-diazabicyclo [4.3.0]non-8-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid-O^3,O^4)bis (acyloxy-O)borate.

Detailed descripion of the Invention: -

The process of the present invention comprises steps as:

- Reaction of Ethyl 1-Cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylate with a mixture of boric acid and acetic anhydride at temperature above 50^{O}C without the use of catalyst

- Separation of (1-Cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid-O^3,O^4)bis (acyloxy-O)borate by cooling to low temperature followed by dilution with water

- Isolation and drying of the (1-Cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid-O^3,O^4)bis (acyloxy-O)borate

- Condensation of (1-Cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid-O^3,O^4)bis (acyloxy-O)borate with (S,S)-2,8-Diazabicyclo[4.3.0]nonane in presence of base(s) in organic polar solvent(s)

- Crystallization of (4aS-Cis)-1-Cyclopropyl-7-(2,8-diazabicyclo[4.3.0]non-8-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid-O^3,O^4)bis (acyloxy-O)borate

- Isolation and drying of (4aS-Cis)-1-Cyclopropyl-7-(2,8-diazabicyclo [4.3.0] non-8-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid-O^3,O^4)bis (acyloxy-O)borate

The prepared 1-Cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid-O^3,O^4)bis (acyloxy-O)borate is a hydrate. The novel

intermediate (4aS-Cis)-1-Cyclopropyl-7-(2,8-diazabicyclo[4.3.0]non-8-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid-O^3,O^4)bis (acyloxy-O)borate is anhydrous. These compounds are characterized by chemical analysis, NMR, FTIR and XRD analysis data.

The starting materials Ethyl 1-cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylate and [S,S]-2,8-Diaza bicyclo[4.3.0]nonane are prepared by literature reported methods.

Acetic anhydride is heated to about 70°C, and boric acid is added in lots. The reaction mass is stirred for about 1hr to about 2 hrs at temperatures of about 70°C - about 125°C, preferably at about 110°C to - about 120°C, cooled to temperature of about 60°C - about 100°C, preferably to about 70°C. To this mixture, ethyl(1-cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylate is added, the temperature raised to about 90°C - about 120°C, preferably to about 100°C - about 110°C and mixed for about 1hr to about 5 hrs preferably for about 1 hr. The reaction mass is cooled to temperature below 35°C, preferably to about 0°C - about 20°C, preferably to about 0°C followed by addition of cold water and then mixed for about 1 to about 4 hrs. The product formed is separated by conventional means, washed with water and dried to obtain 1-Cyclopropyl-6, 7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid-O^3,O^4)bis (acyloxy-O)borate.

(1-Cyclopropyl-6, 7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid-O^3,O^4)bis (acyloxy-O)borate is suspended in organic polar solvents preferably DMSO, DMF, acetonitrile, ethanol and mixed with [S,S]-2,8-diaza bicyclo[4.3.0]nonane in presence of organic, inorganic base(s) preferably triethyl amine, DBU, diisopropyl ethyl amine, potassium carbonate at temperatures about 20°C - about 120°C, preferably at about 60°C - about 80°C for about 1 hr to 6 hrs. After the completion of reaction the reaction mass is cooled and the novel intermediate (4aS-Cis)-1-cyclopropyl-7-(2,8-diazabicyclo[4.3.0]non-8-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid-O^3,O^4)bis (acyloxy-O)borate is separated by removal of solvent under vacuum below 60°C preferably at about 40°C - 45°C followed by addition of the hydrocarbons preferably hexane, heptane, cyclohexane, methyl cyclohexane and mixed for about 2 hrs the product is filtered and dried.

The invention is now illustrated with a few non-limiting examples.

EXAMPLE - I

Stage-1

Acetic anhydride (175 gms) is heated to 70°C and boric acid (30 gms) is slowly added lot wise in a temperature range of about 70°C to about 90°C. The temperature is then raised, maintained under reflux for 1 hr followed by cooling to about 70°C. Ethyl 1-cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylate (100 gms) is added under stirring. The temperature is then raised and maintained for 1 hr in the range of about 100°C to 105°C. The reaction mass is cooled to 0°C, chilled water (400 ml) is added slowly followed by cold water (600 ml) at temperature 0°C to 5°C and maintained for 2 hrs at about 0°C to about 5°C. The product which is a boron acetate complex is filtered, washed with water (500 ml) and dried at about 55°C to about 60°C under vacuum to constant weight.

The dry wt is 130.0 gms corresponding to yield of 95.2%

Stage – 2 :

The boron acetate complex (130 gms) prepared in stage-1 is suspended in acetonitrile (650 ml), and [S,S]-2,8-Diazabicyclo[4.3.0]nonane (47 gms) and triethyl amine (72.9 gms) are added. The temperature is raised to reflux and maintained for 1 hr. at reflux, followed by cooling to about 40°C. The solvent is removed under vacuum at temperature below 40°C, and n-hexane (200 ml) is added. After maintaining the reaction mass for 1 hr at room temperature the product is isolated by filtration followed by washing of the wet cake with n-hexane. The product is dried at about 45°C to about 50°C to constant weight. Dry wt of the novel intermediate is 117.0 gms corresponding to yield of 71.5%.

Elemental analysis: C: 56.42%, H: 5.62%, N: 7.76% and calculated values for the intermediate formula is $C_{25}H_{29}BFN_3O_8$ C: 56.6%, H: 5.47%, N: 7.92%

IR Spectrum (KBr, cm^{-1}): 3415, 3332, 2936, 1718, 1630, 1573, 1526, 1445, 1273, 1042, 935, 860, 798, 682

^1H NMR (200 MHz, $CDCl_3$, ppm): 9.00 (1H), 7.82 (1H), 4.12 (4H), 3.57 (3H), 3.43 (4H), 3.07 (2H), 2.75 (2H), 2.4 (1H), 2.1 (6H), 1.84 (2H), 1.6 (1H), 1.31 (2H)

Mass Spectrum (M^+): 530.3 [M^+H], 470.2 [M^+ - CH_3COOH], 428.2 [M^+-$(CH_3CO)_2O$, 100%], 402.2, 388.2

Claims:

We claim

1. A process for the preparation of a novel intermediate (4aS-Cis)-1-Cyclopropyl-7-(2,8 diazabicyclo[4.3.0]non-8-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid-O^3,O^4)bis (acyloxy-O)borate comprising:

   - Reaction of ethyl 1-cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylate with a mixture of boric acid and acetic anhydride at temperature above 50^{O}C without the use of catalyst

   - Separation of (1-Cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid-O^3,O^4)bis (acyloxy-O)borate by cooling to low femperature followed by dilution with water

   - Isolation and drying of the (1-cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid-O^3,O^4)bis (acyloxy-O)borate

   - Condensation of (1-Cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline .carboxylic acid-O^3,O^4)bis (acyloxy-O)borate with (S,S)-2,8-Diazabicyclo[4.3.0]nonane in presence of base(s) in organic polar solvent(s)

   - Crystallizat of (4aS-Cis)-1-cyclopropyl-7-(2,8-diazabicyclo[4.3.0]non-8-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid-O^3,O^4)bis (acyloxy-O)borate

   - Isolation and drying of (4aS-Cis)-1-cyclopropyl-7-(2,8-diazabicyclo [4.3.0]non-8-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid-O^3,O^4)bis (acyloxy-O)borate

2. A process as claimed in claim 1, wherein the temperature for the reaction of ethyl 1-cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylate with the mixture of boric acid and acetic anhydride is in the range of about 90^{O}C to about 120^{O}C.

3. A process as claimed in claim 1, wherein the organic polar solvents are acetonitrile, DMSO, DMF.

4. A process as claimed in claims 1-3, wherein the base(s) used is organic or inorganic bases

5. A process as claimed in claims 1 & 4 wherein the organic base(s) is triethyl amine, di isopropyl ethylamine, DBU

6. A process as claimed in claims 1 & 5 wherein the inorganic base is potassium carbonate

7. A process as claimed in claim 1, wherein the temperature for the condesation reaction is in the range of about $30^{o}C$ to about $100^{o}C$, preferably from about $60^{o}C$ to about $80^{o}C$

8. A process as claimed in claim 1, wherein the crystallization of (4aS-Cis)-1-Cyclopropyl-7-(2,8-diazabicyclo [4.3.0]non-8-yl)-6-fluoro-8-methoxy -4-oxo-1,4-dihydro-3-quinoline carboxylic acid-O^3,O^4)bis (acyloxy-O)borate is carried out by removal of solvent and addition of a second solvent

9. A process as claimed in claims 1& 8 wherein the second solvent is selected from hydrocarbons of C-5 to C-7

10. A process as claimed in claims 1,8 & 9 wherein the hydrocarbon is alkyl, cycloalkyl or mixtures thereof

11. A process as claimed in claims 1,8,9 & 10 wherein the hydrocarbon is n-hexane, n-heptane, cyclohexane, methyl cyclohexane or mixtures thereof

12. A process as claimed in claim 1, wherein the intermediate (4aS-Cis)-1-Cyclopropyl-7-(2,8-diazabicyclo[4.3.0]non-8-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid-O^3,O^4)bis (acyloxy-O)borate is isolated or without isolation processed for the preparation of moxifloxacin or its salts or hydrates

13. The compound (4aS-Cis)-1-cyclopropyl-7-(2,8-diazabicyclo[4.3.0]non-8-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid-O^3,O^4)bis(acyloxy-O)-borate

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The present invention relates to a method for the preparation of novel intermediate (4aS-Cis)-1-cyclopropyl-7-(2,8-diazabicyclo[4.3.0]non-8-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid-O^3,O^4)bis (acyloxy-O)borate by the reaction of ethyl 1-cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylate with boric acid and acetic anhydride without using any catalyst gives (1-Cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid-O^3,O^4)bis (acyloxy-O)borate which upon condensation in presence of a base(s) with (S,S)-2,8-diazabicyclo[4.3.0]nonane in organic polar solvent results the novel intermediate (4aS-Cis)-1-cyclopropyl-7-(2,8-diazabicyclo[4.3.0]non-8-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid-O^3,O^4)bis (acyloxy-O)borate.

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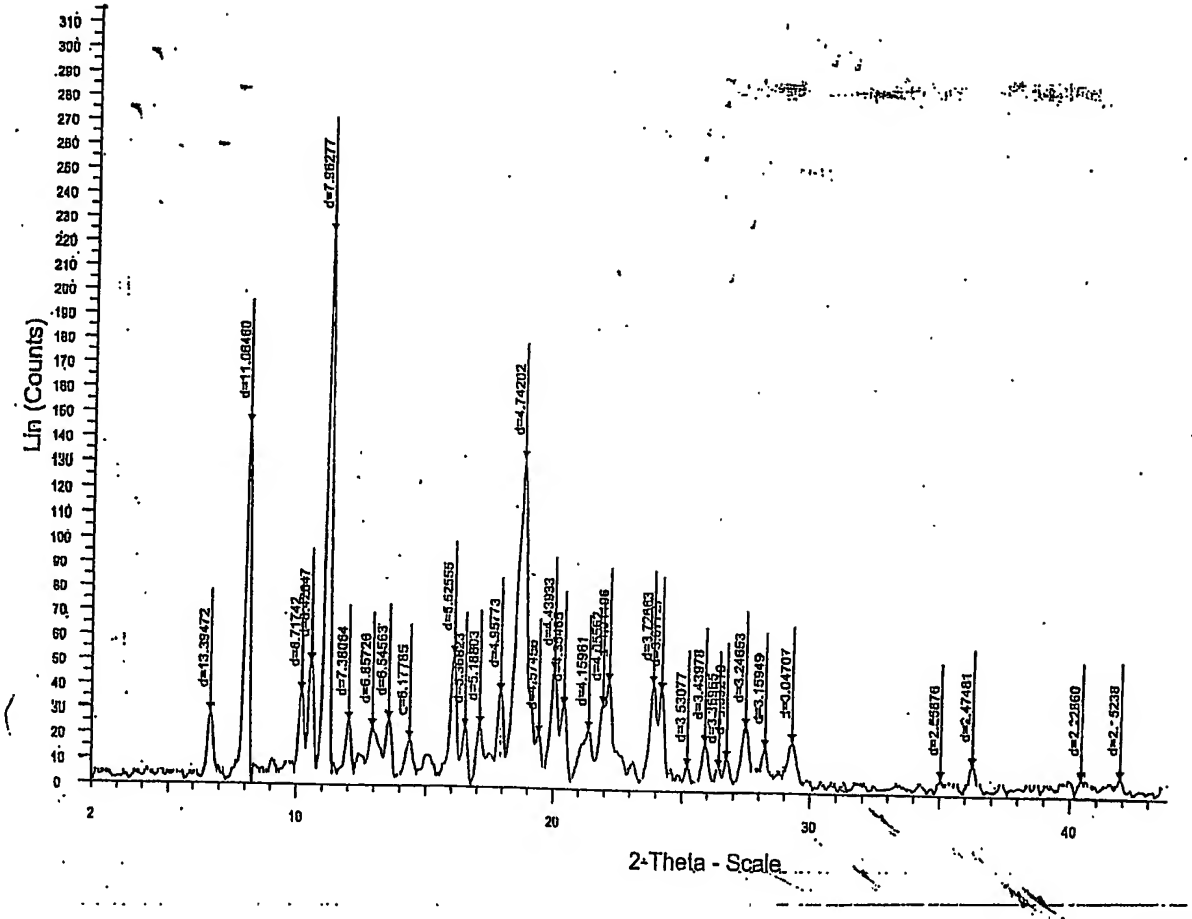

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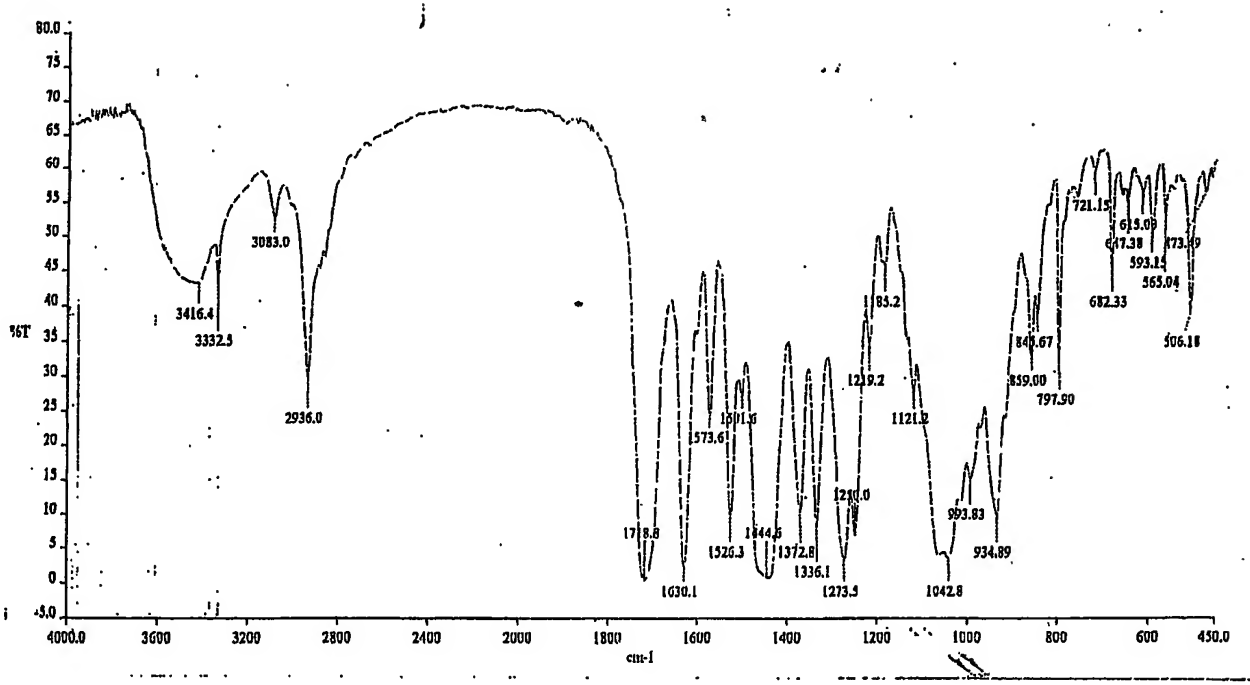

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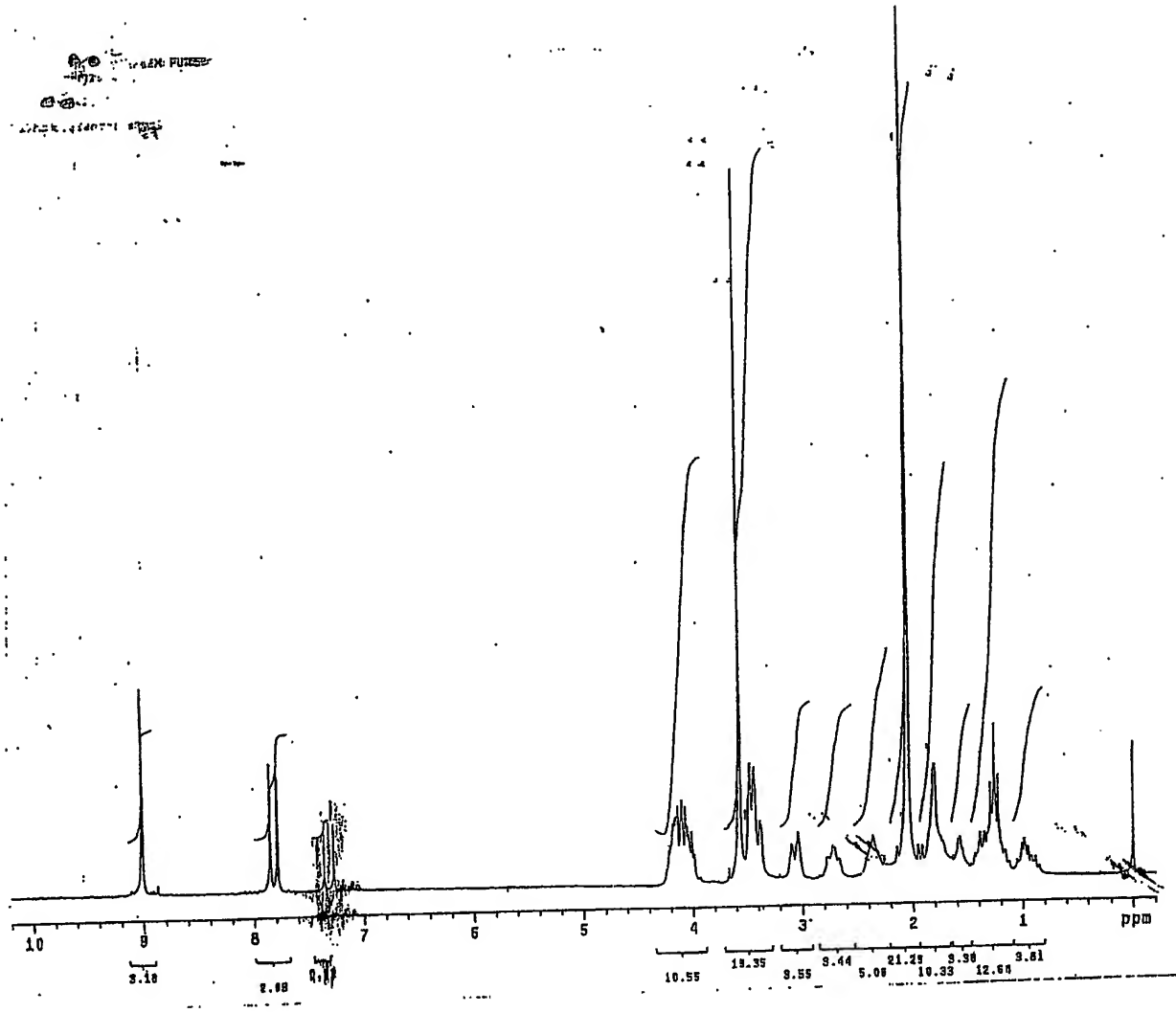
Sheet No 03



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